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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/633,364	FIKES ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004 and 26 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *114,121-131,133-137,139,140,215 and 230* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114,121-131,133-137,139,140,215 and 230* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030710*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The amendment filed February 13, 2004 is acknowledged and has been entered.

2. The amendment filed November 26, 2003 is acknowledged and has been entered. Claims 117, 211-214, and 216-229 have been canceled. Claims 114, 124, 130, 134, 135, and 215 have been amended. Claim 230 has been added.

3. Claims 114, 121-131, 133-137, 139, 140, 215, and 230 are pending in the application and are currently under prosecution.

Information Disclosure Statement

4. The information disclosure filed November 13, 2002 has been considered. In addition, the information disclosure filed July 10, 2003 has been considered. An initialed copy of the PTO Form-1449 submitted with the latter information disclosure is enclosed; the former information disclosure did not include a Form PTO-1449.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment to the claims or the specification has obviated the grounds of objection and rejection set forth in the previous Office action mailed January 29, 2003.

Lack of Compliance with the Requirements of 37 CFR §§ 1.821-1.825

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice to Comply. Applicants must comply with the requirements of the sequence rules (37 CFR

§§ 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

(a) Applicant has not used the proper nomenclature in designating the sequence at positions 1, 3, or 13 of the sequence identified as SEQ ID NO: 6698 at page 54, line 31, since 37 CFR § 1.822 does not provide for the use of "a" and "X" in amino acid sequences; see MPEP § 2423. Because the sequence listing is compliant with the requirements set forth under 37 CFR §§ 1.821-1.825, whereas the specification is not, sequences depicted in the sequence listing and sequences depicted in the specification, which are identified by the same sequence identification number, appear different, since the nomenclature used is different.

(b) In addition, although the sequence listing uses proper nomenclature, the listing of SEQ ID NO: 6698 fails to correctly identify each of the possible residues that can occur at positions 1 and 13 of the sequence. The present listing of SEQ ID NO: 6698 indicates only that the residue at positions 1 and 13 is L-alanine, whereas the specification indicates the residue at positions 1 and 13 is either L-alanine or D-alanine. This deficiency can be corrected by the submission of a substitute sequence listing, which lists the amino acid sequence identified as SEQ ID NO: 6698 as having "Xaa" at positions 1 and 13 and adding information to the description table to indicate that the residues at those positions are either L-alanine or D-alanine.

As noted in the attached Notice to Comply, appropriate actions correcting these deficiencies are required.

Specification

7. As noted in the previous Office action, the specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Another example of an improperly demarcated trademark is Genbank™ (page 10, line 4).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

8. The specification is objected to because of the following informality: At page 1, line 9, the specification reads, "claims the benefit of to Provisional Appln." Deleting "to" can correct the typographical error.

9. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 125 and 139 recite "linker"; however, there does not appear to be antecedent basis in the specification for the claim language "linker" *in its recited context*. It is noted that the term "linker" was recited in the original claim 2 (now canceled). Appropriate action is required; but as a suggestion, Applicant can obviate this issue by deleting "or linker" from claims 125 and 139.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 133 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

Claim 133 recites: "A composition comprising the peptide of claim 114 and a liposome". The specification, including the claims, as originally filed, does not appear to provide proper and sufficient written support for this claim, because the specification, including originally filed claim 6, only provide adequate written support for part of the breadth of the subject matter that is encompassed by claim 133. Claim 6 (canceled) recites: "A composition of claim 1, further comprising a liposome, wherein the epitope is on or in the liposome"; thus, claim 6 fails to provide adequate support for a composition comprising the peptide of claim 114 and a liposome. The disclosure, as originally filed, describes a liposome comprising an epitope or peptide, but fails to describe the claimed invention. Applicant's remarks in the amendment filed July 29, 2002 concerning the whereabouts of support in the specification are noted, but Applicant did not specifically indicate where in the specification support could be found for the limitation recited in claim 133.

This matter might be resolved if Applicants were to point to the particular disclosures in the specification that are believed to provide antecedent basis for recitation of the term in the claims.

12. Claims 114, 121, 122, 124-131, 133-137, 139, 140, 215, and 230 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a peptide less than 15 amino acids in length comprising the 9 amino acid sequence set forth as SEQ ID NO: 6827.

Claims 121 and 122 recite the peptide is 11 or 10 amino acids in length, respectively. Claims 124-126, 215, and 230 recite the peptide is fused to a T helper

peptide epitope, a spacer or linker, or a carrier protein. Claim 127 recites the peptide is fused to a lipid; and claims 131, 133-135, 137, and 140 are drawn to composition comprising the peptide. Claim 129 is drawn to a homopolymer of the peptide.

Claim 130 is drawn to a heteropolymer of the peptide. Absent any guidance to the contrary in the specification, since a protein is a polymer, claim 130 is broadly interpreted to encompass any fusion protein comprising the amino acid sequence of the peptide and a heterologous amino acid sequence.

Claims 128, 135-137, and 139 are drawn to a fusion protein, or a composition of the fusion protein, wherein the fusion protein comprises the amino acid sequence of the peptide and the amino acid sequence or sequences of different proteins. Claims 135 and 137 are drawn to a fusion protein because claim 136, which depends from claim 135, is drawn to recites the peptides form a fusion protein.

The written description of the claimed invention is too inadequate to reasonably convey Applicant's possession of the claimed invention to the skilled artisan; so, it would not appear to the skilled artisan that Applicant actually had possession of the claimed invention at the time the application was filed. The specification describes the peptide of SEQ ID NO: 6827, which binds the MHC class I molecule, HLA-A2.1. The claims, however, are drawn to a broad genus of peptides, homopolymers, heteropolymers, fusion proteins, and compositions, which comprise the amino acid sequence set forth as SEQ ID NO: 6827, but which can vary markedly in both structure and function.

Notably, the members of the claimed genera of peptides or proteins, or the compositions thereof, do not necessarily bind HLA-A2.1; and the functions of even the relatively short peptide members are expected to vary widely with their varying structures. As example, Schoel et al. (*Eur. J. Immunol.* **24**: 3161-3169, 1994) teaches a nonapeptide that is incapable of sensitizing target cells for lysis by a cytotoxic T lymphocyte (CTL) clone, whereas an elongated peptide of 10 or 12 amino acids is capable of stimulating the CTL clone, but an elongated peptide of 11 amino acids is inactive (entire document, but particularly the abstract). Schoel et al. thus demonstrates even short peptides comprising the same core sequence of nine amino acids do not

necessarily share a common function (particularly, the abstract). Accordingly, the members of the genus of peptides or proteins, or the compositions thereof, are expected not to have structures or functions, which are necessarily shared by the disclosed peptide of SEQ ID NO: 6827. Therefore, the peptide of SEQ ID NO: 6827 is not considered representative of the genus as a whole.

Furthermore, it is aptly noted that, even if the members of the claimed genus of peptides were required to bind an MHC molecule, the structurally different members of the genus of claimed peptides would not necessarily bind the same MHC molecule, or stimulate the same CTL clones, since elongating the amino acid sequence set forth as SEQ ID NO: 6827 is expected to produce peptides that bind to MHC molecules other than HLA-A2.1 which would therefore stimulate CTL clones that differ from the CTL clones stimulated by the peptide of SEQ ID NO: 6827. Alternatively, elongating the peptide sequence of SEQ ID NO: 6827 is expected to disrupt binding of the members of the claimed genus of peptides, since such alterations can change the conformation of the peptide to prevent anchor residues contained within SEQ ID NO: 6827 from effecting contacting the peptide binding domain in the cleft of the HLA-A2.1 molecule.

With special regard to claims 128, 130, and 135-137 encompassing a fusion protein, most fusion proteins, particularly relatively large fusion proteins, which comprise the amino acid sequence set forth as SEQ ID NO: 6827, will not bind directly to HLA-A2.1. Therefore these fusion proteins are not expected to share a secondary or tertiary structural feature, or a functional feature that correlates with the presence of the recited amino acid sequence within their primary structures. Therefore, the structural and functional attributes common to at least a substantial number of the members of the claimed genera of proteins or compositions thereof, the presence of which attributes correlates with the presence of the amino acid sequence set forth as SEQ ID NO: 6827 in the protein, have not been described, such that the skilled artisan could immediately recognize, envision, or distinguish the members of the claimed genus from others.

Claim 130 is drawn to a heteropolymer comprising the peptide of claim 114 and "different peptide", whereas claims 135-137 are drawn to a composition comprising the peptide of claim 114 and one or more "other "peptides". Claims 130 and 135-137 thus

encompass enormous genera of peptides and compositions comprising peptides, wherein the peptides other than the peptide of claim 114 are not described to any extent. The other peptides to which the claims refer can have any structure and function; therefore, the written description set forth cannot suffice to adequately describe the claimed invention, such that the skilled artisan would appreciate that Applicant had possession of the claimed invention at the time the application was filed.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an

adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

13. Claims 114, 121-131, 133-137, 139, 140, 215, and 230 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

An analysis of the claims is set forth above.

Notably, the claims do not recite an intended use. The specification, however, teaches the claimed invention can be used to evaluate the immune response against the claimed peptides or proteins, or the claimed compositions thereof, to select CTL epitopes for inclusion in a cancer vaccine; see, e.g., Example 10 at pages 83 and 84 of

the specification. At page 83, lines 23 and 24, the specification teaches epitopes are selected, which upon administration, mimic the immune responses that have been correlated with tumor clearance. However, the specification fails to provide guidance as to which immune responses correlate with tumor clearance and moreover, which epitopes elicit immune responses correlating with tumor clearance. Therefore, to make the claimed invention, the skilled artisan would first have to perform an undue amount of additional experimentation to determine which of the claimed peptides or proteins, and compositions thereof, can be used to stimulate an immune response that correlates with tumor clearance.

The peptide of SEQ ID NO: 6827 has not been shown to elicit an immune response that correlates with tumor clearance, and as evidenced by the teachings of Schoel et al. (cited supra), the skilled artisan cannot predict the effect of altering the length of the peptide of SEQ ID NO: 6827. The teachings of Schoel et al. indicate that adding an amino acid to the produce a ten-mer, for example, may disrupt the ability of the peptide comprising the amino acid sequence of SEQ ID NO: 6827 to bind HLA-A2.1 and to thereby stimulate CTL clones reactive to the peptide, which might lyse tumor cells expressing the tumor antigen prostatic acid phosphatase (PAP), from which antigen the peptide of SEQ ID NO: 6827 is derived. Furthermore, as evidenced by Andersen et al. (*Tissue Antigens* **55**: 519-531, 2000), there is no strong correlation between actual and predicted binding when using predictive computer algorithms (entire document, particularly the abstract). Therefore Andersen et al. concludes, "the peptide binding assay remains an important step in the identification of cytotoxic T lymphocyte (CTL) epitopes which can not be substituted by predictive algorithms" (abstract). Moreover, as evidenced by Feltkamp et al. (*Mol. Immunol.* **31**: 1391-1401, 1994) and Alsheikhly (*Scand. J. Immunol.* **39**: 467-479, 1994), there is poor correlation between binding affinity to class I MHC molecules and the capacity of peptides to induce primary CTL or to serve as potential targets; see the entirety of both documents, particularly the abstracts. Feltkamp et al. concludes that immunogenicity is not guaranteed by efficient peptide-MHC class I binding and therefore additional factors are involved in determining whether a peptide can induce reproducible peptide-specific CTL responses (abstract).

Accordingly, short of making each and every one of the peptides or proteins, or the compositions thereof, which are encompassed by the claims, and empirically determining whether the peptide binds HLA-A2.1 and is capable of stimulating CTL clones that effectively lyse prostate tumor cells to provide tumor clearance, the skilled artisan could not make and use the claimed invention. Therefore, the amount of guidance, direction, and exemplification provided by Applicant's disclosure is not reasonably commensurate in scope with the claims and would not be sufficient to enable the skilled artisan to make or use the claimed invention without having to perform an undue amount of additional experimentation.

Perhaps putting the proverbial cart before the horse, the specification also teaches the claimed invention can be used to analyze the immune response against the claimed peptides or proteins, or the claimed compositions thereof, to determine if a patient has, or can recall CTL clones reactive to the peptide or protein; see Examples 16 and 17 at pages 90-93. The skilled artisan could not use the claimed invention in this asserted manner without first using the claimed invention to stimulate an immune response in a patient. However, as noted above, none of the claimed peptides or proteins, or the compositions thereof, including the peptide of SEQ ID NO: 6827, have been shown to elicit an immune response that correlates with prostate tumor clearance. Therefore, the claimed invention cannot now be used to stimulate an immune response in a patient; and therefore cannot now be used to analyze the immune response against the claimed peptides or proteins, or the claimed compositions thereof, to determine if a patient has, or can recall CTL clones reactive to the peptide or protein.

Nevertheless, it is noted that in Example 16, at page 90, lines 15-17, the specification asserts the example discloses a use for the claimed peptides and proteins, not as immunogens, but as reagents for diagnostic and prognostic purposes. However, if the peptides and proteins are to be used for diagnostic and prognostic purpose in accordance with the guidance set forth by Example 16, the specification is deficient, since it fails to provide guidance as to which diseases or disorders the peptides and proteins can be used as reagents to procure a diagnosis or prognosis. Moreover, the specification fails to teach which, if any of the peptides or proteins comprising SEQ ID

NO: 6827 are associated with the onset, incidence, or progression of any particular disease or disorder, including prostate cancer. Ward (*Developmental Oncology* **21**: 91-106, 1985) teaches, not all markers can be reliably used in primary diagnosis; rather, some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease (abstract). Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable (abstract). Even so, there is insufficient guidance for using the claimed invention as a biomarker. Tockman et al (*Cancer Research* **52**: 2711s-2718s, 1992) teach considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to risk assessment, diagnosis, and/or prognosis of any type of cancer. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, these must be validated against acknowledged disease end points; and, the marker predictive value must be confirmed in prospective population trials (page 2716, column 2).

As an alternative, the specification teaches the claimed invention can be used to determine if a vaccine comprising the claimed invention can be administered safely and

effectively to a patient to treat prostate cancer; see, e.g., Example 18 at page 93. For reasons already addressed above, the process of such a determination itself would require the skilled artisan to perform an undue amount of experimentation, since the skilled artisan cannot predict whether the claimed invention can be used to treat prostate cancer.

Bodey et al. (of record) teaches, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey et al. comments, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). Bodey et al. discloses, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (page 2668, column 2). In the abstract Bodey et al. speculates upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

Thus, little has changed to alter the artisans' expectations of the still prospective immunotherapy since the invention was made.

Regarding whether the skilled artisan can make the claimed invention, the base claim recites a peptide that is at most 14 amino acids in length and comprises SEQ ID NO: 6827. As explained in the rejection of the claims above, as lacking an adequate

written description, the claims encompass a large genus of peptides that vary widely in structure and function. The specification teaches one to make a peptide consisting of SEQ ID NO: 6827, which can be fused to a helper T epitope or a carrier protein. However, the amount of guidance and direction provided by Applicant's disclosure is not reasonably commensurate in scope with the claims, since the specification fails to teach how to make a peptide comprising SEQ ID NO: 6827, which is no longer than 14 amino acids in length and which can be used in the same manner as the peptide consisting of SEQ ID NO: 6827. In addition, claims 130 and 135 recite a heteropolymer or a composition comprising the peptide of claim 114 and other peptides; but since the function and structure of the latter peptides is not described, so as to enable the skilled artisan to make or used the claimed invention, the disclosure is insufficient to meet the requirements set forth under 35 USC § 112, first paragraph. Further regarding claims 124 and 215, the specification fails to teach the skilled artisan to make a T helper epitope, or more particularly a pan-DR binding epitope, other than the T helper epitope and pan-DR binding epitope of SEQ ID NO: 6698, which is incidentally 13 amino acids in length. Therefore, the specification fails to teach the skilled artisan to make a T helper epitope that is no longer than 5 amino acids in length of which the peptide of claim 114 might be comprised.

Concluding, in deciding *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The factual evidence of record shows that at the time the invention was made, even minor structural differences among structurally related compounds or compositions results in substantially different biological and pharmacological activities. Because the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims, Applicant's disclosure of the claimed invention would not be sufficient to enable the skilled artisan to make and use the claimed invention without having to perform an undue amount of additional experimentation.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 124-127, 131, 135-137, 139, 215, and 230 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 124-126, 131, 135-137, 139, 215, and 230 are indefinite for the following reasons: Claim 114 is drawn to a peptide less than 15 amino acids in length comprising the amino acid sequence of SEQ ID NO: 6827, which is 9 amino acids in length. Accordingly, the peptide of claim 114 can comprise at most 5 additional amino acids in addition to the amino acid sequence of SEQ ID NO: 6827. Claim 124 recites the peptide of claim 114 is fused to a T helper peptide; however, it cannot be determined if the T helper peptide of which the peptide of claim 114 is comprised is limited to a peptide having an amino acid sequence that is at most 5 amino acids in length, so that the peptide of claim 114 is no longer than 14 amino acids, or if the peptide of claim 114 is a peptide comprising the amino acid sequence of SEQ ID NO: 6827, at most 5 additional amino acids, and the amino acid sequence of the T helper peptide. If the former, then, claim 230 is indefinite because the T helper peptide of SEQ ID NO: 6698 is 13 amino acids in length, and therefore contrary to the limitation recited in claims 114, the peptide of claim 230 would be 22 amino acids in length. Claims 125, 126, 135-137, 139, and 215 are indefinite for the analogous reasons, namely it cannot be determined if the spacer or linker amino acids, the carrier, the one or more other peptides, or the pan-DR binding epitope of which the peptide of claim 114 is comprised is limited to an amino acid sequence or sequences adding at most 5 amino acids to the length of SEQ ID NO: 6827, so that the peptide of claim 114 is no longer than 14 amino acids, or if the peptide of claim 114 is a peptide comprising the amino acid sequence of SEQ ID NO: 6827 and at most 5 additional amino acids, together with spacer or linker amino acids, the amino acid sequences of the carrier, the amino acid sequences of the one or more other peptides, or the amino acid sequence of the pan-DR binding epitope. Claim 127 is drawn to the peptide of claim 114, which is linked to a lipid; however, because claim 114 is

drawn to a peptide less than 15 amino acids in length comprising SEQ ID NO: 6827, there is no antecedent basis for a peptide fused to a lipid.

Claims 125 and 139 recite "linker"; however, as explained above, there does not appear to be antecedent basis in the specification for the claim language "linker" *in its recited context*. It appears the only disclosures of a linker are in the context of a linking polynucleotide sequence (e.g., page 41, lines 7), as opposed to a linking amino acid sequence. While Applicant may regard "linker" as a synonym of "spacer", there is nevertheless no guidance in the specification as to what constitutes a "linker", as opposed to a "spacer", in the context of the claim. Therefore, the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter that Applicant regards as the invention.

Claims 131 and 137 are vague and indefinite because the claims recite "carrier". The term is given two different meanings in the specification, since a carrier can be a protein carrier, such as thyroglobulin, albumins, hepatitis B virus core protein, and the like, or an aqueous carrier, such as a pharmaceutically acceptable excipient. Because of the duality of the meaning of the term "carrier", the claims are ambiguous and the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter that Applicant regards as the invention.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 130, 135-137, and 140 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Etten et al. (*J. Biol. Chem.* **26**: 2313-2319, 1991), as evidenced by WO 94/20127 A (or record).

Claim 130 is drawn to a heteropolymer of the peptide of claim 114 *and different peptides*, albeit not necessarily heterologous peptides. The claim is broadly interpreted

to read on a protein comprising the amino acid sequence of the peptide set forth as SEQ ID NO: 6827 and the amino acid sequences of other peptides. Similarly, claim 135 is drawn to a composition comprising the peptide of claim 114 and one or more other peptides, and so reads on a protein comprising the amino acid sequence of the peptide set forth as SEQ ID NO: 6827 and the amino acid sequences of one or more other peptides. Claim 136 is drawn to the composition of claim 135, wherein the peptides are fused to form "a fusion protein"; claim 135 is not drawn to a "fusion protein" per se, however, which would ordinarily be understood to be a protein comprising two or more heterologous amino acid sequences.

As evidenced by WO 94/20127 A, SEQ ID NO: 6827 is a fragment of the amino acid sequence of human prostatic acid phosphatase (PAP); see entire document disclosing "Antigen Fragment 180".

Van Etten et al. teaches a complementary DNA (cDNA) clone encoding PAP, which is a protein comprising the amino acid sequence of SEQ ID NO: 6827 and other amino acid sequences; see entire document, particularly the abstract and Figure 3 at page 2316. Van Etten et al. teaches a composition comprising PAP and a pharmaceutically acceptable carrier; see, e.g., page 2314, column 2. Van Etten et al. teaches PAP has a signal sequence that is cleaved to yield the mature protein, which is secreted (Figure 3, page 2316).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 126, 128, 130, 135-137, 139, and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Etten et al. (*J. Biol. Chem.* **26**: 2313-2319,

1991) in view of Zsebo (*J. Biol. Chem.* **261**: 5858-5865, 1986), as evidenced by WO 94/20127 A (or record) and Ostanin et al. (*J. Biol. Chem.* **269**: 8971-8978, 1994).

Claims 126, 128, 130, 135-137, and 140 are drawn to a fusion protein, or a composition thereof, comprising the amino acid sequence set forth as SEQ ID NO: 6827, since claim 114 is drawn to a peptide comprising SEQ ID NO: 6827, which is no more than 14 amino acids, and some other *heterologous* amino acid sequences. Claim 126 recites the peptide of claim 114 fused to a carrier, which carrier can be a heterologous protein; so, claim 126 is also drawn to a fusion protein comprising a peptide comprising SEQ ID NO: 6827 and some other amino acid sequences. Although claim 130 recites "heteropolymer", as opposed to fusion protein, since a protein is a polymer and since the protein of claim 130 is a polymer of the peptide of claim 114 and "different peptides", claim 130 is broadly interpreted to encompass a fusion protein comprising the peptide of claim 114 and different, or heterologous peptides. Claims 135 and 137 are drawn to a fusion protein, because claim 136, which depends from claim 135, recites that the peptides form a fusion protein. Since claim 135 is drawn to a composition comprising the peptide of claim 114 and one or more other peptides, claims 135-137 read broadly on a fusion protein comprising the peptide of claim 114 and different, or heterologous peptides. Claim 139 is drawn to a composition according to claim 135, wherein the amino acid sequence of SEQ ID NO: 6827 and the one or more heterologous amino acid sequences are fused by spacer or linker amino acids.

As evidenced by Ostanin et al., wild-type PAP can be expressed in yeast as a fusion to a leader peptide of prepro-α-factor, resulting in the secretion of processed PAP into the culture medium; see entire document, particularly the abstract and page 8973, columns 1 and 2.

Van Etten et al. and WO 94/20127 A teach that which is set forth above; however, Van Etten et al. does not teach a fusion protein, or a composition thereof, comprising the amino acid sequence of SEQ ID NO: 6827 and one or more heterologous amino acid sequences, which can be fused by spacer or linker amino acids.

Zsebo et al. teaches a method by which many proteins that might be utilized as human therapeutics, which are themselves secreted proteins, can be expressed in yeast and secreted into the culture medium; see the entire document, and particularly the abstract and page 5862, column 1. Zsebo et al. teaches in contrast to directly expressing a recombinant protein in *E. coli*, which often yields analogs of the natural protein with amino-terminal methionine or *N*-formyl methionine, their method enables the production of recombinant proteins with authentic amino-termini (page 5862, column 1). Zsebo et al. teaches the production of an in-frame fusion protein comprising prepro-α-factor and another protein, and optionally a spacer peptide, which can join the sequence of the prepro-α-factor and the sequence of the other protein; see, e.g., page 5859, column 1. Zsebo et al. teaches a composition comprising the fusion protein and a pharmaceutically acceptable carrier, i.e., "Bufflayte 4-8/Cl (Pierce)"; see, e.g., page 5863, column 2.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to express PAP, as described by Van Etten et al., using the method described by Zsebo et al., and in doing so, to make a fusion protein comprising PAP, a spacer, and prepro-α-factor and also produce compositions comprising the fusion protein and "Bufflayte 4-8/Cl", because Zsebo et al. teaches any protein, which are themselves secreted proteins, can be expressed in yeast and secreted into the culture medium using their methodology, whereas Van Etten et al. teaches provides a cDNA molecule encoding just such a protein, namely PAP. One ordinarily skilled in the art would have been motivated to do so to express PAP using the expression of system disclosed by Zsebo et al. to produce the PAP.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 114, 121-128, 130, 131, 133-137, 139, 140, and 215 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 and 23-25 of copending Application No. 10/168,507. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims are drawn to nearly the same compositions. Although none of the copending claims recite a composition comprising a pharmaceutically acceptable carrier, copending claim 24 recites a vaccine comprising a pharmaceutical excipient. Although none of the copending claims recite a fusion protein or a heteropolymer, copending claim 10, for example, recites the composition comprises an epitope, i.e., a peptide having the same amino acid sequence as the peptide of SEQ ID NO: 6827, joined a linker; and the peptide joined to a linker is interpreted to be the same as the fusion protein of instant claim 128 or claims 135-137, or the heteropolymer of instant claim 130. Although the copending claims do not recite a carrier, copending claim 11, for example, recites the composition comprises a epitope bound to carrier proteins, namely HLA heavy chain, β2-microglobulin, and streptavidin complex. Furthermore, copending claim 14 is drawn to a clonal cytotoxic T lymphocyte that is cultured in the presence of a peptide having the same amino acid

sequence as the peptide of SEQ ID NO: 6827, thus again rendering instant claim 114, for example, obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
June 10, 2004

Christina Chan
CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No.	Applicant(s)	
	09/633,364	FIKES ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Please see the Office action for an explanation of the specific deficiency. If necessary to correct the deficiency, Applicant is required to submit substitute copies of the sequence listing and the statement, as indicated below.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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